ELSEVIER

Cognitive Brain Research 11 (2001) 127–145

COGNITIVE BRAIN RESEARCH

www.elsevier.com/locate/bres

Research report

Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks

Jeanne Townsend[a,b,*], Marissa Westerfield[b,c], Echo Leaver[b,d], Scott Makeig[e,f], Tzyy-Ping Jung[c,e], Karen Pierce[a,b], Eric Courchesne[a,b]

[a]*Department of Neurosciences 0217, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0217, USA*
[b]*Research on the Neuroscience of Autism, Children's Hospital, San Diego, CA, USA*
[c]*Institute for Neural Computation, University of California, San Diego, La Jolla, CA, USA*
[d]*Department of Psychology, University of Illinois, Urbana-Champaign, IL, USA*
[e]*The Salk Institute, La Jolla, CA, USA*
[f]*Naval Health Research Center, San Diego, CA, USA*

Accepted 24 October 2000

Abstract

Although under some conditions the attention-related late positive event-related potential (ERP) response (LPC) is apparently normal in autism during visual processing, the LPC elicited by visuospatial processing may be compromised. Results from this study provide evidence for abnormalities in autism in two components of the LPC generated during spatial processing. The early frontal distribution of the LPC which may reflect attention orienting was delayed or missing in autistic subjects during conditions in which attention was to peripheral visual fields. The later parietal distribution of the LPC which may be associated with context updating was smaller in amplitude in autistic subjects regardless of attention location. Both abnormalities suggest disruption of function in spatial attention networks in autism. Evidence that the cerebellar abnormalities in autism may underlie these deficits comes from: (1) similar results in ERP responses and spatial attention deficits in patients with cerebellar lesions; (2) brain–behavior correlations in normally functioning individuals associating the size of the posterior cerebellar vermis and the latency of the frontal LPC; and (3) a previously reported complementary correlation between the size of the posterior vermal lobules and spatial orienting speed. Although the scalp-recorded LPC is thought to be cortically generated, it may be modulated by subcortical neural activity. The cerebellum may serve as a modulating influence by affecting the task-related antecedent attentional process. The electrophysiological abnormalities reported here index spatial attention deficits in autism that may reflect cerebellar influence on both frontal and parietal spatial attention function.

Theme: Neural basis of behavior

Topic: Cognition

Keywords: Spatial attention; Autism; Cerebellum; Frontal cortex; ERP; P300

1. Introduction

1.1. Brain structural abnormalities in autism

Autism is a pervasive developmental disorder in which there is severe disruption of cognitive and social function. The complex pattern of brain abnormalities in autism suggests that function may be affected by both cortical and subcortical pathology. Autopsy and in vivo studies of brain structure in autism have consistently reported abnormalities of the cerebellum. Post mortem studies have found reduced numbers of Purkinje neurons in the cerebellar vermis and cerebellar hemispheres [9–12,43,106,127]. The amount of loss typically ranges from about 20–60% with a distribution that is patchy and varies across the cerebellar hemispheres and vermis in individual autistic cases. In total, cerebellar anatomic abnormality is present in 95% of all autism autopsy cases, making this the single most

*Corresponding author. Tel.: +1-858-551-7928; fax: +1-858-551-7931.
E-mail address: jtownsend@ucsd.edu (J. Townsend).

0926-6410/01/$ – see front matter
PII: S0926-6410(00)00072-0

common biological abnormality known for this disorder (for review see [32]).

Consistent with the post mortem findings are quantitative MRI studies of several hundred autistic subjects from eight independent research groups that have found hypoplasia of cerebellar vermal lobules VI–VII in these individuals, (e.g., [18,21,22,25,35,36,45,53,62,65,78,93,99,108]). (Note: for a discussion of controversial findings in [65] and [99], see [36]). A few studies have reported no difference between autism and control subjects in cerebellar vermis [44,55,100]. A small number (10–12%) of individuals with autism have extreme overgrowth (hyperplasia) of the posterior cerebellar vermis [34–36].

Structural abnormalities in the brainstem, and in parietal and frontal cortex have also been reported [9,18,33,53]. Carper and colleagues have found an association between the size of the posterior vermis and abnormal enlargement of frontal lobes in young autistic children [18]. Children with the greatest cerebellar hypoplasia had the greatest overgrowth of frontal cortex. The limbic system is another common site of anatomic abnormality. In MRI studies, autistic patients have reduced amygdala volume [8] and reduced cross-sectional area of the dentate gyrus [109]. In autopsy studies, anatomic abnormality in limbic structures is present in most [12], but not all [9], autism cases. When present, limbic system abnormality involves increased density of neurons and reduction in neuron sizes [12].

1.2. ERP abnormalities in autism: the LPC

Abnormalities of scalp-recorded event-related potential (ERP) responses have been consistently reported in individuals with autism. Among these are the attenuation or absence of attention-related frontal negativities, and reduced amplitude of the late positive complex (LPC), largely comprised of the P300 (for reviews see [24,26]). It has generally been concluded that these abnormalities are electrophysiological evidence of abnormal and less efficient attentional processing.

Both the fronto-centrally distributed P3a which is elicited by novel stimulation and the parietally maximal P3b which is elicited by attended information are abnormal in autism. Significant attenuation of the P3b in individuals with autism has most often been found in auditory attention tasks, or in response to the omission of an auditory or visual stimulus from a sequence [20,29–31,39,79,89,94–96]. However, studies using a simple visual target discrimination with stimuli presented in central vision have generally found no difference between autism and normal subjects in the amplitude of the P3b response to targets [20,30,31,105].

Although under some conditions the visual LPC appears to be normal in autism, the LPC elicited by visuo-spatial processing may be compromised. Verbaten et al. [119] found a significantly smaller P3b in autism over all electrode sites when subjects counted a visual target presented at various peripheral visual locations. Unfortunately, the interpretation of these results is not entirely clear since fewer than half of the autism subjects performed the task correctly and as a group the autism subjects failed to show differences in responses to targets and non-targets. In a similar spatial task, Kemner et al. reported smaller P3b in autism subjects over occipital sites only [63]. In this task, however, the probability of the target stimulus was 40% and there appear to be no attention-related effects for autism or normal control subjects.

Autism is only one of a number of diverse clinical disorders with different neural pathology in which the LPC is abnormal. These disorders include schizophrenia, depression, attention deficit disorder, dyslexia, alcoholism and multiple sclerosis (for review see [98]). The LPC has also been reported to be reduced in amplitude and extended in latency with normal aging in which it is characterized by a changed scalp topography that may reflect loss of frontal inhibition (for reviews see [19,101]).

1.3. Major components of the LPC

The LPC is not unitary, but is formed by the spatial and temporal overlap of multiple components with multiple generators, (for reviews see [69,98,102]). Some components may be task or modality specific, while others may reflect a common attention-related process. One of the most widely accepted models is that the P3b reflects mental record keeping — the updating of information held in working memory [40]. An interesting alternative is that the P3b may reflect completion of processing a perceptual task and an associated release of neural inhibition that follows task resolution [54,72,114,120]. Of course, completion of a perceptual task would be likely to require a working memory update so that both models could be reflected in components of the LPC.

Three separate components of the LPC can be consistently identified from averaged ERP data (for reviews see [69,98,103]). An early fronto-centrally maximal response that is similar to the novelty P3a [28,115] may be elicited initially to a rare (low probability) target stimulus and may be associated with attention orienting [66,103]. The early response is followed by the parietally maximal P3b which is followed in turn by a more posterior positive slow wave [66,103]. Using Independent Components Analysis (ICA), Makeig has identified three robust ICA-components of the LPC associated with a visuospatial task [86]. These are: an early frontally positive ICA-component with bilateral parietal negativities at the most lateral scalp sites (ICA-P3f) that may reflect spatial orienting; a centroparietal positive ICA-component with a right frontal bias (ICA-P3b) that is most similar to the attention-related P300 described in ERP literature; and a late posterior maximal slow wave that reverses polarity over the central

sulcus (ICA-Pmp, post motor potential) and reflects motor processes (e.g., the button press response).

1.4. Possible brain sources of the LPC

There is now reasonable consensus that the scalp-recorded LPC is cortically generated, although it may be modulated by subcortical neural activity. Intracranial recordings, lesion studies and source modeling have been used in attempts to localize potential generators (for review see [50]). Lesion study results are consistent with dissociation of LPC components and suggest different generators for separable components. Lesions to the temporal-parietal junction significantly reduce the auditory P3b but affect the visual P3b in non-spatial tasks only slightly [69,71,121]. In contrast, the early, fronto-centrally distributed positivity (P3a) elicited by novel stimuli in any modality is significantly reduced by lesions to either prefrontal or posterior cortex [66,68,69,71]. Posterior hippocampal lesions also attenuate the fronto-central P3a, but do not affect the P3b [67,70]. Our recent data suggest that the LPC elicited in a visual-spatial task may differ from that produced in a non-spatial visual task. We found that patients with lesions involving the temporal-parietal junction (TPJ) had a slightly reduced visuospatial LPC. In this same study, patients with unilateral lesions involving the intraparietal sulcus (IPS) had a more dramatic result with no discernible LPC. Patients with frontal or posterior lesions that did not involve the TPJ, the IPS, or white matter tracts underlying the IPS, had LPC responses that were normal in amplitude and latency [42]. Subcortical lesions can also affect the LPC. Thalamic lesions may prolong the latency of the LPC, but do not reduce the amplitude [97]. Akshoomoff and Courchesne [2] reported reduced amplitude LPC in patients with cerebellar damage in a non-spatial attention shifting task. Yamaguchi also found reduced amplitude LPC in patients with cerebellar degenerative disorder during a spatial shifting task [128]. Our recent data also show a reduction of the visual LPC in a spatial task in patients with unilateral cerebellar lesions [124,126]. This reduction is particularly prominent over frontal electrode sites — an abnormality that may reflect the effect of the cerebellum on frontal attention orienting systems.

1.5. Autism and spatial attention orienting: cerebellar involvement

There is evidence for abnormal attention shifting and orienting in autism and in cerebellar lesion patients. For example, autistic individuals and cerebellar lesion patients are slow to shift attention between and within sensory modalities and are slow to orient attention in space [1,37,52,116–118]. On spatial cueing tasks (e.g., [104]), individuals with autism and those with acquired cerebellar damage are quite slow to orient to a cued location [116–118]. Once their attention is oriented, however, these individuals perform simple visual discrimination tasks as quickly and as accurately as control subjects. In a recent study when individuals with autism were asked to discriminate a stimulus in the visual periphery that was presented briefly then masked, they were able to do so as well as normal control subjects if they were given a second or more to orient attention to the stimulus location. With only 100 ms to orient attention to the stimulus location, the accuracy of control subjects was greater than 90%, but autism subjects performed at near chance levels. A group of patients with acquired damage to the cerebellum were also slow to orient attention on this task. An index of the speed with which attention could be oriented was found to be significantly correlated with the size of cerebellar vermal lobules VI–VII [116]. Because this task assessed the accuracy of a simple perception and not the speed of a motor response, it provided an index of the speed of attention orienting that was not confounded with slowed motor response.

In contrast to these findings, however, from a study of patients with degenerative cerebellar disorder Yamaguchi et al. reported that damage to the lateral cerebellum does not affect spatial attention shifting [128]. The task in this study was an attentional cue (either central or peripheral) followed by a simple target to detect. Their conclusion was based on behavioral data in which normal control subjects showed a larger decrease in reaction time (RT) with more time to shift attention than did the patients, and on ‘comparable modulation’ of early sensory responses in the patients and control subjects. There are several possible explanations for the differences between our results and those of Yamaguchi et al. The first is that the Yamaguchi et al. study used RT as the behavioral dependent measure for attention shifting and the RT for patients was significantly longer than that of control subjects. Long response times could mask attentional effects. Our results were based on perceptual accuracy. Second, in the Yamaguchi et al study, the longest interval in which to shift attention was 800 ms. Our data [116] suggest that this interval is not long enough for an attention shift in cerebellar lesion patients. In the Yamaguchi et al. study there was little or no improvement in RT in patients with 200 ms vs. 500 or 800 ms delays in which to shift attention. In contrast, the control subjects showed a significantly shorter RT with 500 ms compared to 200 ms to shift attention (a typical result). No change in the patient RT with longer attention shift intervals implies that they have either fully shifted attention within 200 ms (which control subjects did not) or that by 800 ms they have not yet shifted attention.

Finally, the Yamaguchi et al. study reported that 800 ms after a central cue the N1 to attended targets was larger than the N1 to unattended targets in both patients and control subjects (the N1 would reflect attention-related sensory enhancement and would suggest that attention had been shifted to the cued location within 800 ms). Their

conclusion was that this reflected a normal (or better than normal) attention shift with 800 ms. There are a number of problems with this conclusion. First, this is the only condition in the study in which there were any early sensory (P1 or N1) effects of attention for either control subjects or patients. This suggests that there may have been inadequate power to observe the typical P1/N1 indices of spatial attention. In fact, in each condition there were a maximum of 67 valid trials and 17 invalid. This number of trials is very unlikely to produce stable data for the early sensory components. A similar study [88] used more than 10 times as many trials in young normal subjects to produce stable attentional effects in early sensory components (P1 and N1). In the one condition (central cue) for which the N1 was larger to targets at the validly cued location, the waveforms to the cue suggest that there was directional eye movement so that at target delivery, gaze was shifted toward the cued location (this is particularly apparent in the patient group). The N1 is significantly larger in foveal vision. If subjects moved their eyes to the cued location, the N1 amplitude would reflect a gaze shift, not an attention shift (for a discussion see [88]).

Although attention orienting is a processing function that has generally been associated with cortical function, there is evidence to suggest that such function can be affected by damage to subcortical systems. For example, lesions or disease processes that affect the basal ganglia produce a variety of behavioral deficits that are also associated with direct damage to regions of frontal cortex [38]. Lesions confined to the cerebellum have been also reported to disrupt a number of processes normally associated with frontal lobe function including planning, problem solving, working memory and affect [1,15,17,49,75–77,112,122]. Additionally, lesions to the cerebellum have been reported to produce metabolic abnormalities in frontal and parietal cortex (crossed cerebellar diaschisis) [7,16,64,107]. Functional magnetic resonance (fMRI) studies have shown activation of the cerebellum in normal individuals during shifting attention [74], attention tasks that were independent of motor involvement [3], and spatial cueing tasks [23].

Studies examining neural pathways between the cerebellum and cerebral cortex have reported pathways that may provide the means by which the cerebellum may affect spatial attention systems. Neuroanatomic studies by Strick and colleagues have demonstrated multiple output pathways from the deep cerebellar nuclei to distinct regions of cerebral cortex [91,92]. These studies detail anatomic connections from specific regions of the dentate nucleus that project via the thalamus to premotor and prefrontal cortex that are separate from those that project to primary motor cortex. The posterior parietal cortex receives cerebellar input via the pulvinar as well [6,14]. Posterior parietal input [110] to the cerebellum is via the pontine nuclei as a part of the mossy fiber tract. Through this same pathway, the cerebellum receives input from both striate and extrastriate visual cortex [46,123]. However, only the portions of visual and prefrontal cortex that are concerned with the peripheral visual field, visual spatial parameters, and visual motion project to the pons (and via the pons to the cerebellum), as opposed to regions concerned with the central visual field and visual object identification [111].

Results from our studies of autism and cerebellar lesion patients suggest that the cerebellum affects spatial attention orienting. This study was designed to examine components of the event-related late positive complex (LPC) that reflect attentional processes that may be impaired with cerebellar damage in conjunction with behavioral and brain structural data. To that end we recorded behavioral performance and event-related potentials generated during a visual spatial attention task from individuals with autism and age-matched normal control subjects upon whom we had quantitative structural brain data from magnetic resonance imaging (MRI). We hypothesized that early frontocentral components of the LPC that may be associated with attention orienting would be abnormal in the autism subjects, and that in normal control subjects these waveform components would be associated with MRI measures of the cerebellar vermis.

2. Materials and methods

2.1. Subjects

Nine high-functioning male subjects with autism and 14 age-matched male control subjects participated in the study. Participants with autism all met DSM-III-R or DSM-IV [4,5] criteria for autistic disorder. Seven subjects also received the Autism Diagnostic Interviews, ADI or the ADI-R [73,82] the Autism Diagnostic Observation Schedule, ADOS or the ADOS-6 [80,81] and all subjects received the Childhood Autism Rating Scale, CARS, [113]. None of the autism subjects met diagnostic criterion for Asperger's syndrome. None had additional psychiatric or neurological diagnoses. All participants with autism were screened for the presence of fragile X syndrome and all were found to be negative. Subjects with autism are from a group with abnormal cerebellar vermal lobules VI–VII [36].

Normal control participants were volunteers recruited from the community. Controls had no history of substance abuse, special education, major medical or psychiatric illness, developmental or neurologic disorder. A previously published independent components analysis (ICA) study of a larger sample of normal subjects included data from these 14 control subjects [86]. Diagnostic scores for the subjects with autism are presented in Table 1. Ages and IQ scores for the subject groups are presented in Table 2.

2.2. Task

The basic visual display was five dimly illuminated one

Table 1
Scores from diagnostic tests for subjects with autism[a]

Subj	Age	CARS	ADI Social	ADI V com	ADI Nv com	ADI RepBeh
1	16	39	28	21	14	7
2	21	35.5	30	16	14	11
3	22	45	30	20	13	6
4	25	39	25	16	9	9
5	30	36.5	26	20	14	6
6	32	42.5	29	22	12	11
7	33	36	21	22	12	10
8	38	30				
9	38	32.5	21	9	6	4
Mean	28.33	37.33	26.26	18.25	11.75	8.00
S.D.	7.8	4.7	3.7	4.4	2.9	2.6

[a] Criterion scores to meet autism diagnosis for ADI subscales are: Social=10; Verbal communication (V com)=6; Nonverbal communication (Nv com)=7; Repetitive behaviors (RepBeh)=3. Individuals with CARS scores in the range 30–36 are considered mildly to moderately autistic and those with scores greater than 37 are considered to be severely autistic.

inch square boxes displayed in a row, 1/2 inch above the horizontal center of a 14 inch video monitor (see Fig. 1). At the center of the screen a bright cross (1/2 inch in height and width) served as a fixation point. The five boxes were evenly spaced so that with subjects seated 34 inches from the screen the visual angles of peripheral boxes were 3 and 6 degrees to the left and right of the center box. Filled white circles, one half inch in diameter, were presented for 100 ms in the center of one box at a time. During a block of trials a blue outline marked the location to be attended, and all circles presented in that box were targets. All circles presented in the four remaining boxes were non-targets. The circles were presented randomly in equal numbers at each of the five locations so that target probability was 20%. All five locations served as an attended location. The order of blocks for each attended location was counter-balanced across subjects, but blocks were randomized only once so that all subjects received the same set of randomized stimulus sequences. Inter-stimulus-intervals (ISIs) were varied from 225 to 1000 ms and selected randomly from equally spaced intervals (a rectangular distribution).

Table 2
Age and IQ scores for subject groups, from WAIS-III, WAIS-R, or WISC-R[a]

	Normal controls	Autism
n	11	9
Age (S.D., range)	26.82 (7.6, 16–39)	28.33 (7.8, 16–38)
VIQ (S.D.)	122.18 (14.3)	77.11 (11.0)
Vocabulary (S.D.)	13.8 (3)	4.3 (1)
Comprehension (S.D.)	13.5 (5)	3.4 (2)
PIQ (S.D.)	116.27 (9.9)	89.55 (12.4)
Block design (S.D.)	12.4 (2)	11.0 (3)
Object assembly (S.D.)	12.6 (3)	10.2 (3)

[a] IQ scores were available for only 11 of the 14 normal control subjects. Ages for the entire sample of 14 normal control males ranged from 16 to 39, mean=27.21±7.0.

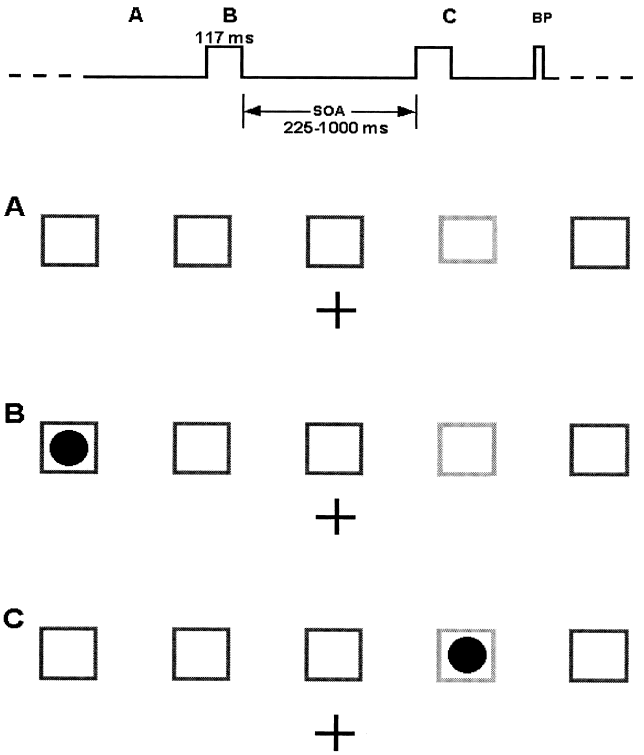

Fig. 1. This diagram of the task shows: (A) the basic five-box visual display with location to be attended highlighted (Box 4); (B) a non-target stimulus in Box 1; (C) a target stimulus in the attended location (Box 4).

Subjects were instructed to press a button when the circles (target stimuli) appeared in the attended box, and to ignore the circles (non-target stimuli) that occurred in boxes at the other four (unattended) locations. A button press response 150–1200 ms following a target circle was scored as a correct response (hit), and no response during that same time window following a target circle was scored as a miss. A button press to a non-target circle (i.e. if there was no target circle in the 150–1200 ms preceding the press) was scored as a false alarm. For each of the five attended locations, subjects completed 3–5 blocks of 100 trials.

2.3. MRI procedures

MRI data acquisition protocols, segmentation and measurement methods for cortical volumes are detailed in Courchesne et al. [27]. That manuscript also reports a validation study for the automated segmentation methods. For these measures, a dual echo PD- and T2-weighted axial imaging sequence was performed in a 1.5-T GE Signa MR scanner. Following an automated correction for signal fall-off and a semi-automated removal of skull and extra-cranial structures, a fully automated segmentation algorithm was used to classify all pixels into gray matter, white matter or CSF. Cerebellar area measurements were from manual tracings done by expert anatomists on mid-sagittal (4 mm) T1-weighted images as described in Courchesne et al. [35].

2.4. ERP recording procedures

Electroencephalographic (EEG) signal was recorded from 29 channels with electrodes placed at scalp sites Fz, F3, F4, FC1, FC2, FC5, FC6, T7, T8, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, POz, PO3, PO4, PO7, PO8, Oz, O1, and O2 according to the International 10-20 System. Vertical and horizontal EOG was recorded in order to detect eye movement artifacts (i.e. blinks and saccades). EOG electrodes were placed at the left outer canthus (LC) and below the right eye (RLoe). All electrodes were referenced to the algebraic average of the unlinked right (the recording reference) and left mastoid electrodes. EEG was amplified using a bandpass of 0.01 to 1000 Hz, lowpass-filtered at 50 Hz, then digitized online at a rate of 256 sample points per second. ERP data were processed and analyzed off-line using software developed in the Hillyard laboratory at the University of California, San Diego (ERPSS, J.S. Hansen). Additional analyses were conducted with software developed by Makeig, Jung, Sejnowski and colleagues at the Salk Institute and the University of California, San Diego (Independent Component Analysis, ICA, see http://www.cnl.salk.edu/~scott/icafaq.html) [56,58,59,83–85].

2.4.1. Artifact correction

Because many autistic subjects have difficulty controlling eye and muscle movement, contamination from artifact in their ERP data can be a serious problem. A common procedure is to detect artifacts due to blinking, muscle activity, or eye movement and then to eliminate epochs found to be contaminated with any one of these artifacts from further processing and analyses. If too many trials are eliminated a subject's data may be unusable. If artifact is not eliminated, it is impossible to interpret data accurately. This is a particularly serious issue in spatial attention designs where distracting peripheral stimuli may consistently elicit saccadic shifts. Alternative methods for correcting eye movement that use regression models to adjust levels of activity at electrode sites thought to be most contaminated may distort or mask the signal, particularly at anterior recording sites(for a discussion of this issue see [58,60]). A new method using single-trial ERP data and Independent Component Analysis (ICA, [13]) has been used effectively to correct heavily contaminated ERP data without introducing the distortions of data over anterior electrodes that may occur with regression model correction algorithms [56–58,60,61]. The ICA method uses spatial filtering to decompose multiple-channel EEG data into spatially-fixed and temporally independent components. Since sources of artifact have a spatial distribution and time-course that is independent of those for EEG activity, ICA can derive independent, separable components for these artifactual potentials and extract them from the real (non-eye, non-muscle) brain sources of electrical activity (i.e. the true EEG signals). That is, the potentials accounted for by different independent components at a single time-point are independent. This definition of independence allows independent components to account separately for similar activities occurring in different brain areas at different time lags or frequencies, or even at the same frequency if their phases are not coherent [58].

Artifact removal from our data was a two-step process. First, we rejected epochs for trials in which the amplifiers were blocked and trials that contained eye artifact during a window starting 200 ms before, and extending through, stimulus presentation. This ensured that we did not retain epochs of data during which the subject may not have seen the stimulus. The remaining single trials in each of the target conditions were concatenated and submitted to an ICA decomposition [83,84,86]. Components were selected in each subject that accounted for eye or other muscle artifact and those rows in the activation matrix were set to zero. The data sets were then reconstructed (without the contribution of the artifact components), and the 'artifact corrected' data were averaged and measured [56–58,60]. Jung et al. [60] demonstrates the efficacy of this method applied to some of this data, and shows examples of artifact-correction in individual subjects. The ICA-corrected data is very similar to the most lightly contaminated raw data, suggesting that ICA correction has not distorted the original brain electrical signal.

2.4.2. Averaged ERPs

Averages of artifact-corrected epochs were made for each stimulus type (i.e. target, nontarget at each location) and categorized by the associated behavioral response (i.e. hit, miss, false alarm, correct rejection) for each subject at each attended location. The peak amplitude and latency of the late positive complex (LPC) were measured at all 29 EEG electrode sites over a time interval of 300–600 ms post stimulus with a baseline computed over the 50 ms prior to stimulus delivery.

2.4.3. Statistical analysis of averaged ERPs

ANOVAs examining group differences in LPC latency and amplitude (measured from artifact-corrected data) were initially carried out using all 29 electrode sites and all five attend locations (two groups×29 electrodes×five attend locations). To interpret interactions, these two ANOVAs were repeated with attended location as attend center or attend peripheral (average of locations 1, 2, 4, 5), and with electrodes averaged across larger anatomic regions as follows: frontal (F3, Fz, F4), fronto-central (Fc1, Fc2), central (C3, Cz, C4), centro-parietal (CP1, CP2), parietal (P3, Pz, P4), parieto-occipital (PO3, Poz, PO4), and occipital (O1, Oz, O2). There were no differences in results from analyses using a reduced number of factor levels, so only the simpler analyses (seven electrode regions and, except where noted, two spatial attention conditions). Follow-up contrasts were done using error variance from these ANOVAs to compare latency and

amplitude at frontal and parietal electrode sites. Analyses reported used target epochs, but analyses of difference waves (target–nontarget) produced essentially the same results.

2.4.4. Single trial measures

For each subject, measurements were taken at Pz in 200 trials centered around that subject's median RT. Amplitude measures were the average positive amplitude for each trial over the 200 ms following the response. A measure of variability for each subject was the standard deviation of the amplitude across the 200 trials. These measures were analyzed for group differences in both mean and variability. Fig. 2 displays these sets of single trials as a series of erpimage plots [59]. These plots are color representations of individual epochs (100 ms pre-target to 900 ms post-target) for the 200 trials. Amplitudes of the ERP response are color coded (positive red, negative blue). Trials are ordered by speed of response (i.e. trials with shortest RT are at bottom of the plot). The solid black 'S' curve shows RT at each trial.

2.4.5. Independent components analysis (ICA)

Group averaged data (uncorrected data) were decomposed using ICA. Averages of 1 s ERP epochs to standard and target stimuli at the five locations (i.e. five spatial

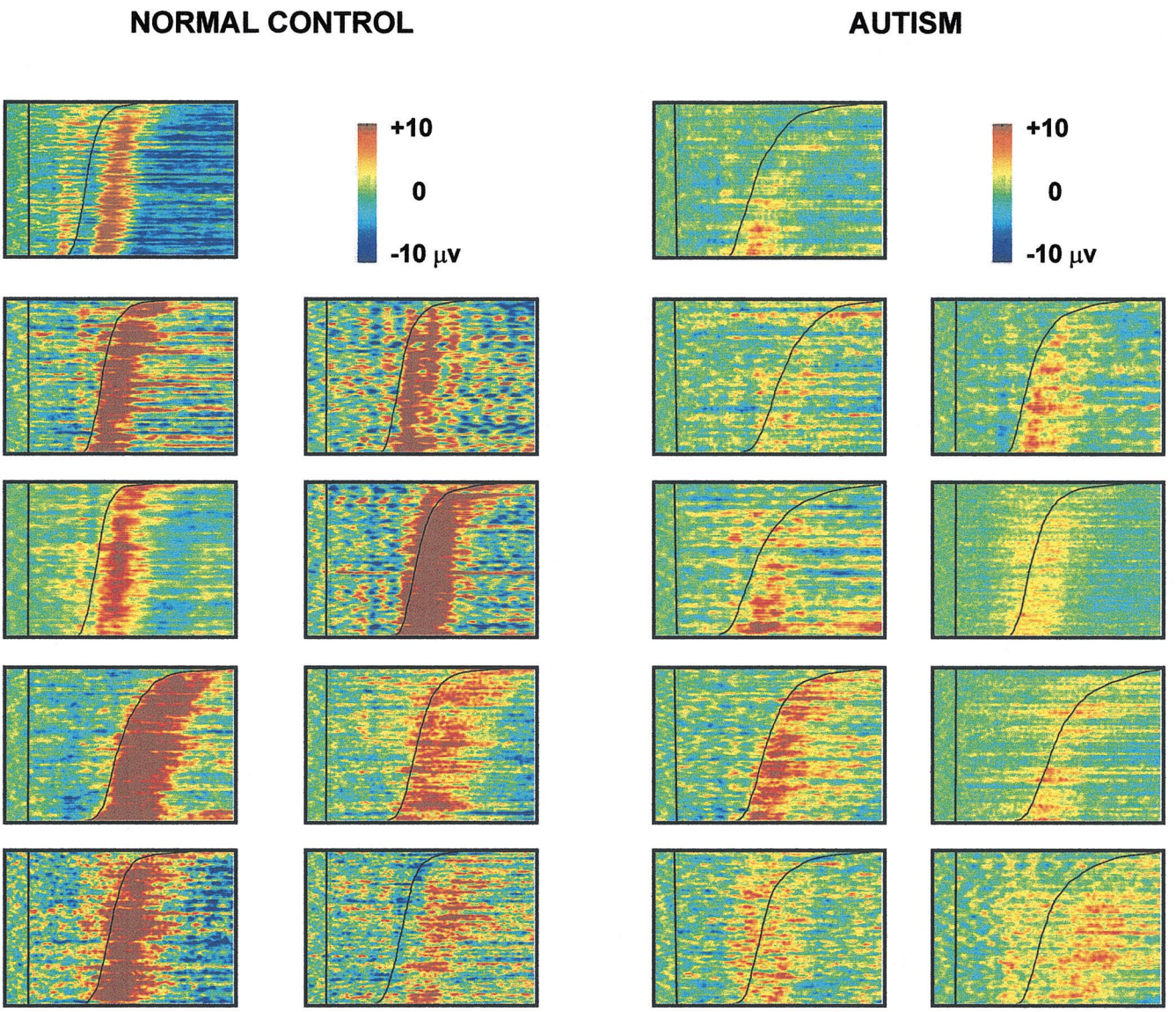

Fig. 2. This ERPIMAGE plot [59] shows single trial data for the nine autism subjects (on right) and age-matched normal control subjects (on left). Subjects are ordered within group by age with youngest subjects at the top of the plot. These plots are color representations of individual epochs (100 ms pre-target to 900 ms post-target) for the 200 single trials centered around each subject's median RT. Amplitudes of the ERP response are color coded (positive red, negative blue). Trials are ordered by speed of response (i.e. trials with shortest RT are at bottom of the plot). The black 'S' curve marks RT. Note that while there is variability in the LPC response of control subjects, most display a robust positivity following the response (the LPC). In autistic subjects the LPC is present on fewer trials, and is reduced in amplitude where present.

attention conditions) were calculated for each group. This resulted in 25×1 s traces (averaged across subjects within a group) for each group (autism and controls) for the 31 electrode channels (note EOG channels were included for the ICA decomposition so that components associated with eye movement artifact would be identified separately, and to extend topographic coverage over anterior regions). These traces were concatenated and decomposed using the ICA toolbox [86]. This analysis yielded 31 independent components for each group. These components represent independent combinations of temporal patterns across the one second epoch and spatial distributions of the electrical signal over the 31 channel field.

3. Results

3.1. IQ data (see Table 2)

Autism subjects had significantly lower scores on measures of verbal IQ, performance IQ, and verbal subscales assessing vocabulary and comprehension (all $t_{16}>5.00$, $P<0.01$). There were no significant differences between autism and control subjects for the performance subscales in which individuals with autism typically demonstrate normal ability, block design and object assembly.

3.2. Anatomic data from MRI (see Table 3).

For seven of the nine autism subjects cerebellar vermal lobules VI–VII were significantly smaller than in control subjects ($t_{19}=3.58$, $P<0.002$). Two of the autism subjects showed hyperplasia of lobules VI–VII. Autism individuals with hypoplasia had vermal lobules VI–VII that were 18% smaller than controls, while those with hyperplasia had measures that were 30% larger than controls (controls: 293.9±47, hypoplastic autism: 240.5±21, hyperplastic autism: 380.8±2). In such a skewed distribution, the mean is inordinately influenced by the extreme scores, and does not represent the bulk of the cases accurately (70% of normal control subjects fall above the median of the entire sample, while 78% of those with autism fall below the sample median, χ^2 (1)=4.70, $P<0.02$).

Table 3
Means and (S.Ds) from magnetic resonance imaging (MRI) quantitative estimates

	Normal control	Autism
n	14	9
Cerebellum (mm^2)		
Vermal lobules I–V	481.16 (39.2)	456.23 (51.7)
Vermal lobules VI–VII	293.89 (46.8)	271.65 (64.6)
Brain volume (ml)		
Intracranial	1466.8 (126)	1535.5 (112)
Total brain	1289.9 (113)	1307.3 (95)
Total gray	835.5 (85)	835.9 (78)
Total white	454.4 (56)	471.4 (39)
Total CSF	177.1 (58)	228.2 (60)

With age covaried, autism subjects had significantly more whole brain CSF than did control subjects ($F_{1,20}=5.80$, $P<0.026$). There were no other differences in brain volume or area measures.

3.3. Behavioral accuracy and response time (RT)

Autism subjects were less accurate than controls overall ($F_{1,21}=26.10$, $P<0.0001$; mean percent hits for autism=84.2±9, controls=96.5±2). Subjects with autism were less accurate when attending peripheral visual fields than when attending the center location, but there was no difference in accuracy of control subjects as a function of the attended location (group by attended location interaction, $F_{4,84}=9.61$, $P<0.008$).

There were fewer than 1% false alarm responses overall, and no difference between groups in the rate of false alarm responses. Both groups of subjects had a higher false alarm rate to non-target stimuli in locations adjacent to the attended location than to non-target stimuli in non-adjacent locations ($F_{1,21}=8.67$, $P<0.008$).

Subjects with autism were slower to respond to attended stimuli than were controls regardless of location ($F_{1,21}=6.32$, $P<0.025$; mean RT for autism=406.0±47, for controls=356.9±45). Both groups responded faster to attended stimuli at the center location than at peripheral locations ($F_{1,21}=35.84$, $P<0.0001$; mean RT at center=357.8±46, at peripheral locations=380.8±53).

3.4. Late positive complex (LPC) averaged ERP latency

Latency of the LPC peak was shorter over frontal than over parietal regions in normal control subjects, but frontal and parietal peak LPC latency were not different in autism subjects. There was no overall difference between groups in the peak latency of the LPC. There was, however, an interaction of electrode and diagnostic group ($F_{6,126}=3.71$, $P<0.025$; see Fig. 3). The peak latency of LPC was shorter over anterior than over posterior electrode sites ($F_{1,13}=7.76$, $P<0.02$) in normal control subjects, but was not different at frontal and posterior sites in the autism group. Additionally, during peripheral attention, peak LPC latency over frontal electrode sites was longer for autism than for control subjects ($F_{1,21}=6.46$, $P<0.02$), but was not different between groups at parietal electrode sites. There was no difference between groups in latency (overall or at anterior or posterior sites) in the attend center condition. Differences in latency and amplitude (see results below) at frontal and parietal sites are summarized in Fig. 4.

Over frontal electrode sites, in the 14 normal control subjects, the peak latency of the LPC was shorter in those with larger cerebellar vermal lobules VI–VII ($r=-0.61$, $P<0.02$), but only when the attended location was in the

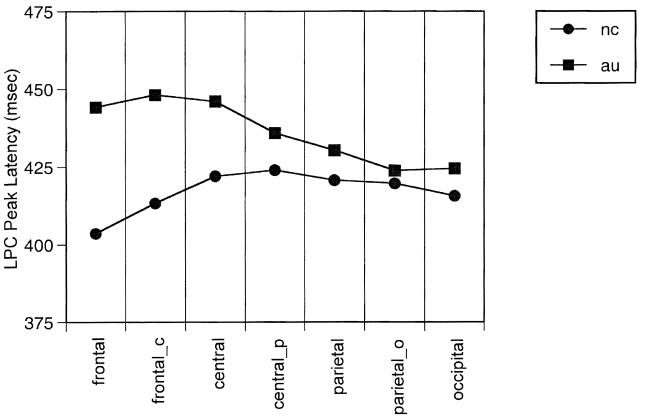

Fig. 3. LPC latency in autism and control groups as a function of electrode site.

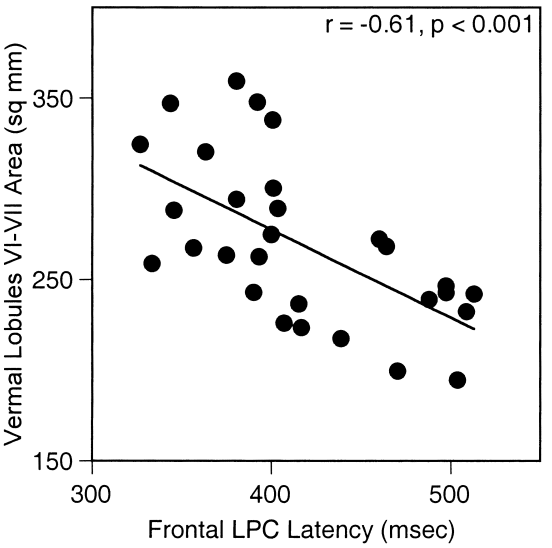

Fig. 5. Correlation in larger normal sample of cerebellar vermal lobules VI–VII (area quantified from magnetic resonance images, see Materials and methods) and frontal LPC latency. These are all control subjects for whom data from this task and quantified MRI measures were available ($n=29$, subjects aged 16–82). These subjects have served as part of a study of electrophysiology of normal spatial attention function [86,87], and have served as control subjects for focal lesion and autism groups in our studies of spatial attention.

peripheral visual field. We repeated this analysis with a larger group of normal control subjects ($n=29$, subjects aged 16–82). The correlation was also significant in this larger group, ($r=-0.61$, $P<0.001$, see Fig. 5). There were no significant relationships (or trends): between vermal lobules I–V and LPC latency over frontal electrode sites; between vermal lobules VI–VII and LPC latency when the attended location was at center; or with vermal lobules and LPC amplitude. This was true for both the smaller sample that serves as the control group for the autism subjects in this study, and for the larger normal control sample. There was also no significant relationship between vermal size and frontal LPC latency in autism subjects.

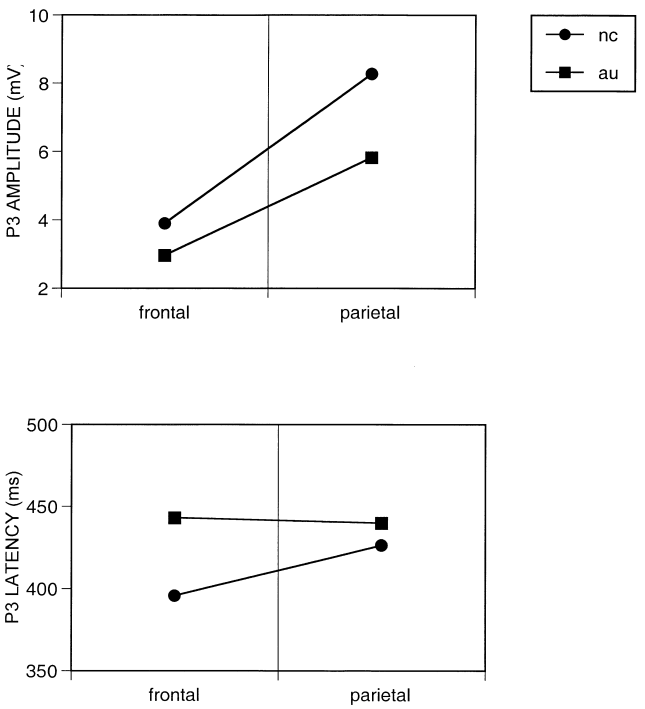

Fig. 4. Summarizes LPC latency and amplitude differences between autism and control subjects at frontal and parietal electrode sites during peripheral attention conditions. Frontal measures represent peak latency or amplitude averaged over electrodes F3, F4 and Fz. Parietal measures represent peak latency or amplitude averaged over electrodes P3, P4 and Pz. All measures represent LPC latency and amplitude averaged across the four peripheral attention conditions (two left, two right).

3.5. Late positive complex (LPC) averaged ERP amplitude

Fig. 6 shows ERP responses to targets for control and autism subjects at all electrode sites. For comparison with autism subjects, Fig. 7 shows waveforms from a group of patients with acquired cerebellar lesions (data from [124,126]).

Over electrode sites and across target locations, there was a trend for smaller peak amplitude LPC to correctly identified (attended) targets in the autism group overall ($F_{1,21}=3.26$, $P<0.085$). There was no difference between groups in peak LPC amplitude over frontal sites, but there was a significant group difference at parietal electrode sites ($F_{1,21}=4.71$, $P<0.05$). Additionally, all subjects showed greater peak amplitude responses when attending the center compared to peripheral locations ($F_{1,21}=12.55$, $P<0.002$), and larger peak amplitude over parietal electrode sites ($F_{6,126}=19.4$, $P<0.0001$). Over all parietal electrode sites, and at Pz, where the LPC was maximal in both subject groups, peak LPC amplitude was significantly smaller in autism subjects ($P<0.05$).

In normal control subjects there was no difference in

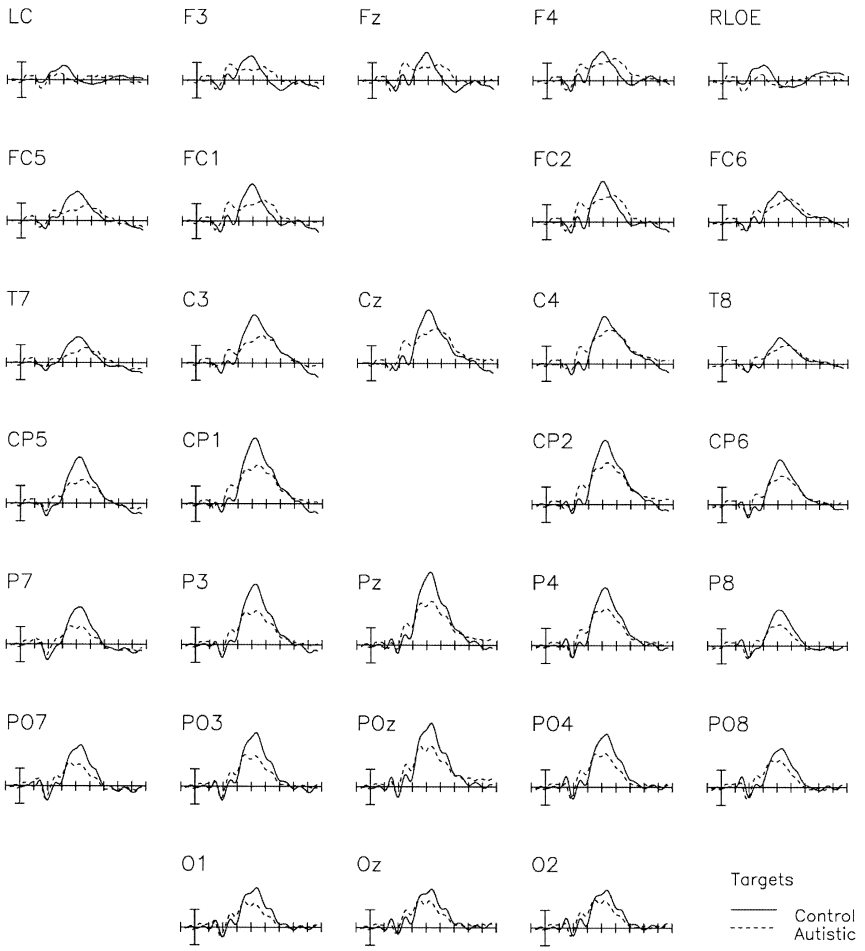

Fig. 6. Averaged ERPs to correctly identified targets for autism (dashed line) and normal control subjects (solid line). Data are averaged across the five attend locations. Vertical lines mark the time of stimulus delivery and show a 2 μV calibration with positive responses plotted up. Horizontal axis tick marks represent 100 ms intervals.

peak LPC amplitude over anterior electrode sites as a function of attended location, but over posterior scalp sites LPC peak amplitude was larger in the attend center condition. In autism subjects, however, the difference in the LPC peak amplitude when attending the center relative to the periphery was constant across all electrode sites (three-way interaction of electrode, attended location and diagnostic group, ($F_{6,126}$=5.22, P<0.009). Fig. 4, presented above with LPC latency results summarizes frontal and parietal differences between groups in both peak amplitude and latency during peripheral attention conditions.

3.6. Single-trial analysis of the LPC

Fig. 2 shows erpimage plots for all autism and nine age-matched control subjects at the central parietal electrode site (see Materials and methods). Results from analysis of the single trial measures were consistent with results from averaged ERPs. Autism subjects showed smaller amplitude LPC at Pz (t_{21}=4.12, P<0.0008). Single trial variability (within subject standard deviation across the 200 single trials) of average LPC amplitude at Pz was greater for control subjects than for autism subjects (t_{21}=3.32, P<0.005). This result may seem inconsistent with a visual inspection of Fig. 2 in which the inconsistency of the LPC response in the autism subjects is notable. However, the single trial variability was greater for control subjects because the amplitude range across trials was considerably greater for control subjects (1–17.5 μV vs. 1.7–5.7 μV in autism). The median percent of trials on which average LPC amplitude was greater than 1 μV was 90% for control subjects and 74% for autism subjects. Control subjects generated LPC responses that were greater than 5 μV on approximately two-thirds of the single trials, while autism subjects generated responses that large on only one-third of the single trials. This is consistent with visual inspection of Fig. 2.

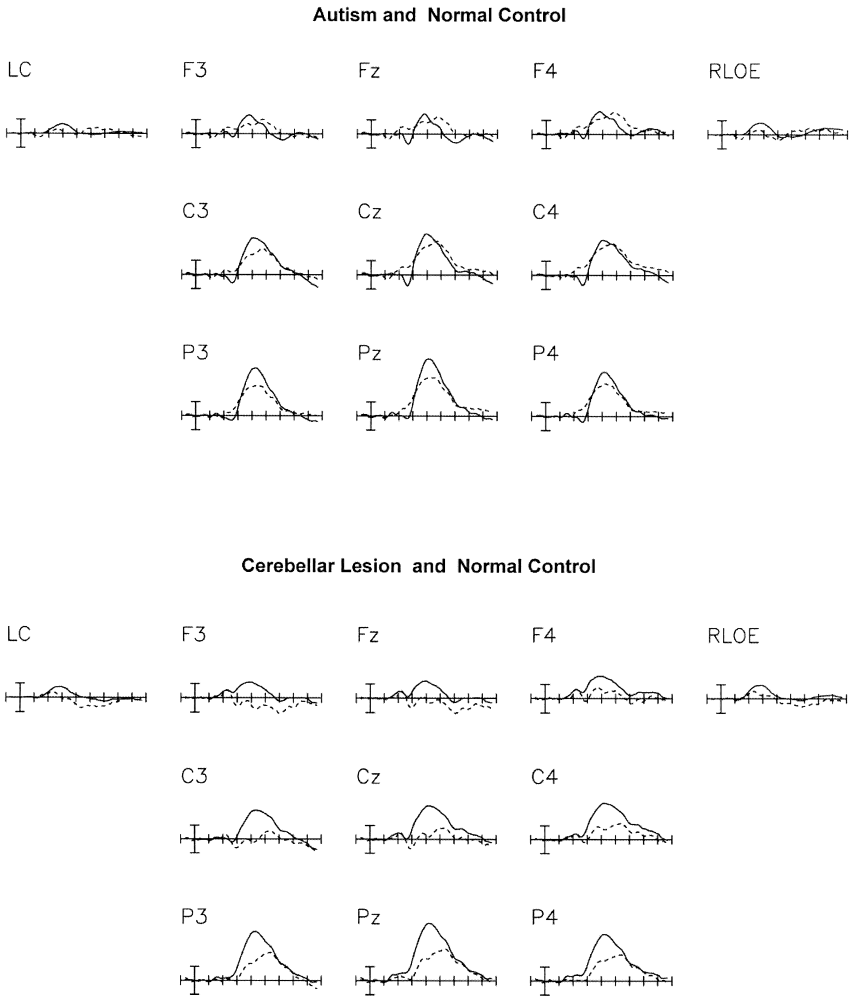

Fig. 7. LPC in autism (dashed line) and control subjects (solid line) (TOP) and in cerebellar lesion (dashed line) and age-matched control subjects (solid line) (BOTTOM) from the same spatial attention task used with autism subjects in the study reported in this manuscript. Shown here are difference waves calculated by subtraction of nontargets at a given location from targets at the same location. Difference waves are collapsed across the five attend locations. Vertical lines mark the time of stimulus delivery and show a 2 μV calibration with positive responses plotted up. Horizontal axis tick marks represent 100 ms intervals. From [124,126]. Lesion patients are described in [116].

3.7. Independent components analysis (ICA)

Independent Components Analysis decomposition of the averaged ERP data for control and autism groups is shown in Fig. 8. Three major components were extracted from the LPC in each group — explaining 98.4% of variance in the control data, and 92.1% of the variance in the autism data. Components are named following Makeig et al. [86]. Temporal patterns show that compared to controls, the earliest component (P3f) is smaller in the autism group and has a different spatial distribution. This component has a prominent posterior positive focus in both groups. In controls, there is a broad frontal positive response that is attenuated or missing in the autism group. The P3b component is smaller in the autism group, but the component spatial topography is quite similar in both groups. The later slow wave Pmp component is also somewhat smaller in autism subjects. The posterior focus of this component in the autism group has an anterior shift and is missing the frontal negative response that is prominent in the control Pmp component.

4. Discussion

Behavioral performance and electrophysiological responses during spatial attention suggest that use of covert attention is impaired in autism. Two components of the attention-related late positive electrophysiological response were abnormal in individuals with autism. Early frontal LPC responses that reflect attention orienting were delayed and performance was reduced during attention to peripher-

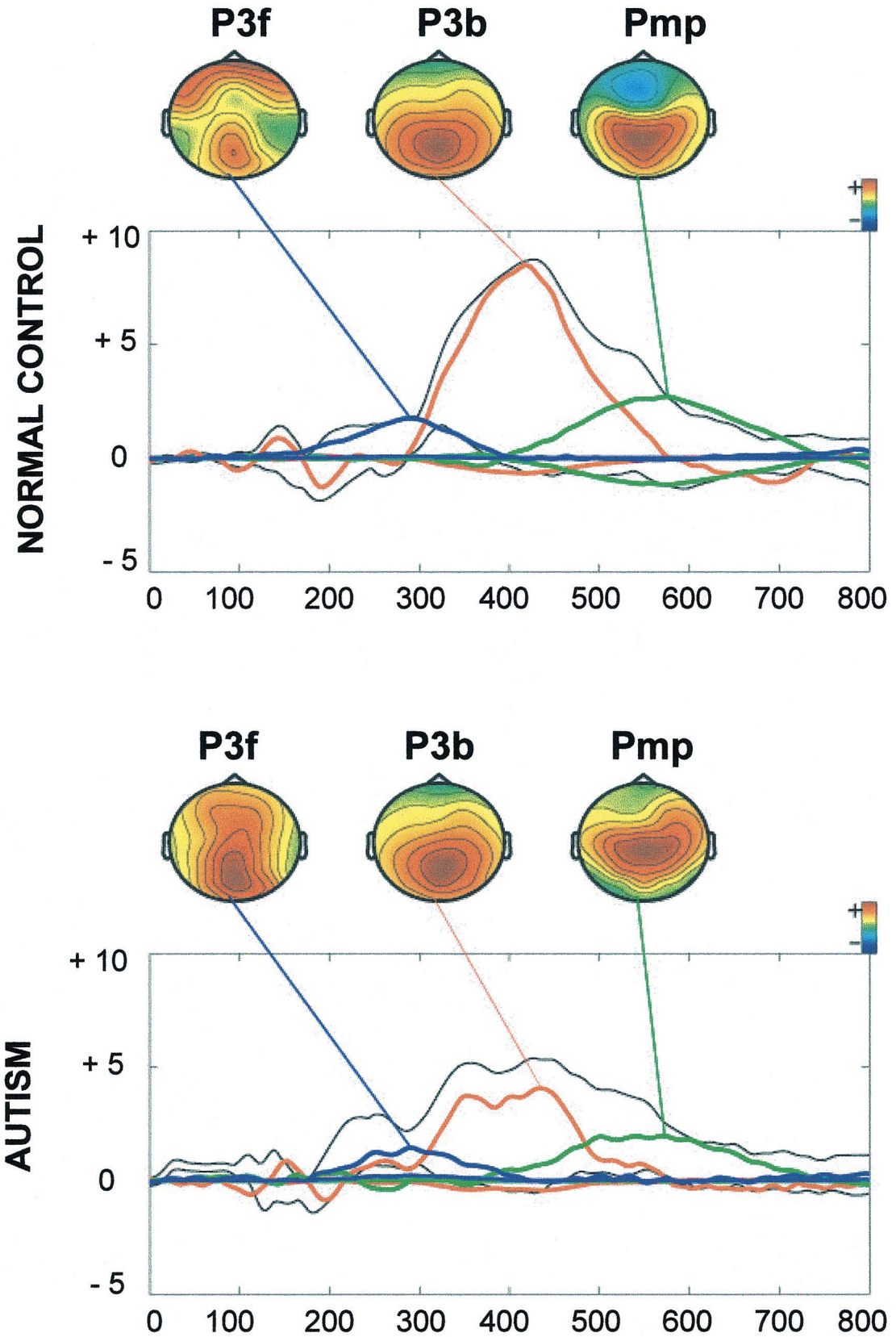

Fig. 8. ICA decomposition showing three major components of the LPC in control and autism groups. Spatial maps show the distribution of the component (red positive, blue negative). Traces show activation across the epoch. Component traces resemble averaged ERP waveforms, but are representations of the component activation across the 1000 ms (800 shown) with fixed spatial distributions (activity at all 31 electrode sites). Components are superimposed upon an envelope (solid black line) from the averaged ERP data, displaying positive and negative boundaries of all channels.

al visual fields. Later, parietally maximal LPC responses which may be associated with context updating were smaller in amplitude. Both abnormalities suggest disruption of function in spatial attention networks in autism, and may reflect cerebellar influence on frontal and parietal spatial attention systems.

4.1. The anterior late positive complex (LPC): attention orienting

In control subjects, as is commonly the case, the frontal LPC preceded the larger posterior waveform. In autistic subjects the frontal LPC was significantly later, and peaked at the same time over both frontal and posterior regions. This late peaking frontal response in autistic individuals may reflect a delayed component, or may reflect a severely reduced or missing early component. In either case, this abnormality in a component that may represent attention orienting is consistent with these subjects' reduced accuracy to targets in the visual periphery and is also consistent with our previous findings of impaired attention orienting in autism [52,116–118]. When attention was to the visual periphery, the latency of the frontal LPC was significantly earlier in normal individuals with larger posterior cerebellar vermal lobules. This correlation was specific to covert spatial attention as there was no relationship between frontal LPC latency and the posterior vermis in attend center conditions. This correlation was specific to the posterior vermis as there was no relationship between frontal LPC latency and anterior vermal lobules that support motor function, or with measures of total brain volume. This correlation was also specific to the frontal LPC as there was no correlation with vermal lobules and the latency of the posterior LPC. Finally, there was no corresponding correlation in autistic subjects, perhaps because frontal LPC latency measures in autistic subjects reflect the time-course of the posterior not the anterior component. This association of larger vermis and early frontal LPC latency is consistent with our earlier reports of faster attention orienting in those with larger posterior vermal lobules [116] and may be an electrophysiological index of the same attention orienting process.

Latency differences in both control and autism subjects point to different components in the frontal and posterior distribution of the LPC. The early frontally distributed and the subsequent parietally maximal manifestations of the LPC are separable. These components can be disrupted independently and are likely to have different brain sources, although these sources may be overlapping. These components also reflect different cognitive processing stages. The early frontal component may reflect attention orienting, while the later parietal component has been proposed to reflect context updating or perceptual closure. The early frontal component is similar to the novelty P3a response [28,115], and may represent activation of the same or overlapping generators as the novelty response. That is, any infrequent target stimulus may initially elicit a P3a-like component that is associated with orienting attention to that event [66,103]. In our data, the latency of this component is associated with the size of a brain structure that has also been associated with speed of orienting attention. The later posterior LPC does not have the same relationship to brain structural measures, and doesn't index location.

Independent components analysis of our data also supports separable components and has identified three robust LPC components with unique spatial and temporal characteristics in each group. In the control subjects these components are nearly identical to those identified by Makeig in a larger sample during this same visuospatial task [86]. These are: an early frontally positive component with bilateral parietal negativities at the most lateral scalp sites (ICA-P3f) that may reflect spatial orienting; a centroparietal positive component with a right frontal bias (ICA-P3b) that is most similar to the attention-related P300 described in ERP literature; and a late posterior maximal slow wave (ICA-Pmp, post motor potential) that reflects motor processes (e.g., the button press response). The ICA components reflect the integration of information from all 31 electrode sites over the entire 1 s ERP epoch. All three components are reduced in amplitude in subjects with autism. Spatial topography of the ICA-P3b component is nearly identical in autistic and control subjects, but topography of the ICA-P3f and ICA-Pmp components differs. The ICA-Pmp in autistic subjects is missing the frontal negativity that is prominent in the control response. There is a concomitant anterior shift in the positive focus of the autism Pmp component which seems consistent with the prolonged late positive slow wave seen over frontal sites in the averaged ERP data for this group. The autism ICA-P3f lacks the prominent frontal positivity of the control component. While the ICA-P3f component peaks earlier than the averaged ERP frontal LPC, the failure of the frontal positivity in the autism group at the LPC onset is also consistent with the reduced or delayed LPC peak over frontal sites in the averaged ERP data.

There is considerable evidence for disruption of both the P3a and P3b components as a result of damage to specific brain regions, but the location of source generators for these components are still unknown. The early frontal component is affected by damage to pre-frontal or posterior association cortex or the hippocampus [69]. Even if scalp recorded LPC components are cortically generated, the response can clearly be affected by brain structures remote to the generating source. Halgren has suggested that one of the difficulties in source localization of a complex waveform is that the recorded response can be affected not only by the generating structure, but also by 'trigger' or 'antecedent' structures. For example, an ERP response may be severely attenuated or abolished by lesions to the generating structures, but may also be affected by damage to 'trigger' or 'antecedent' structures

[50,51]. Damage to a trigger structure would be expected to affect a larger region than that affected by direct damage to the propagating structure. Damage to an antecedent structure would be expected to alter task-related responses specifically. In visuo-spatial function, the cerebellum may serve as an antecedent structure, influencing the frontal generation of the P3a during attention orienting.

There is ample evidence that cerebellar damage can affect cortical function. For example, altered metabolic activity in frontal and parietal cortex (crossed cerebellar diaschisis) is seen following cerebellar lesions [7,16,64,107]. Lesions confined to the cerebellum can disrupt a number of processes normally associated with frontal lobe function including spatial and non-spatial working memory [1,15,17,49,75–77,112,122]. In normal individuals, functional magnetic resonance imaging (fMRI) studies have shown activation of the cerebellum in conjunction with cortical regions during spatial attention [23]. Neuroanatomic connections between the cerebellum and prefrontal cortex are consistent with cerebello-frontal interaction in spatial attention function. Interestingly, Schmahmann has reported that only portions of the visual cortex and prefrontal cortex concerned with the peripheral visual field project to the cerebellum (via the pons) [111].

Evidence that the cerebellum may serve as an antecedent structure in the generation of the frontal LPC during spatial attention processing comes from several sources. First, our data from normal control subjects shows a significant correlation between the size of posterior vermal lobules VI–VII and: (1) the speed of spatial attention orienting [116]; (2) the latency of the frontal LPC. In both cases, larger vermal lobules are associated with faster spatial orienting. Results from recent fMRI studies of normal spatial attention function also suggest that during visuo-spatial attention the cerebellum is consistently active in concert with cortical structures known to be active during spatial attention processing [23]. Second, during spatial attention tasks, the frontal LPC is effectively absent over anterior sites in patients with acquired brain lesions that directly affect only the cerebellum (see Fig. 7). Third, in autistic individuals who have developmental abnormalities of the cerebellum, the frontal LPC response during visuo-spatial attention is either severely delayed or absent. In subjects with autism, the delayed latency of the frontal LPC could reflect a delayed frontal response, or alternatively, that response could be missing or severely attenuated so that the peak response observed over anterior scalp sites does not reflect a separate component, but the later parietally maximal P3b. A similar result has been found in patients with cerebellar lesions [124,125]. In both clinical groups there was a severe attenuation or absence of the early frontal LPC. Finally, both cerebellar lesion patients and individuals with autism are abnormally slow to orient or shift visual spatial attention [116].

Although the cerebellum is the most consistently reported site of brain abnormality in autism, brain abnormality in autism is not confined to the cerebellum. There is evidence from structural MR imaging for abnormality in frontal and parietal cortex and in the limbic system in some autistic individuals [8,9,12,18,33,109]. Delayed or absent P3a responses in autism could then result from abnormal cortical and not abnormal cerebellar function. This seems unlikely since there is a similar result from cerebellar lesion patients and a significant relationship between cerebellar vermal area and frontal LPC latency in normally functioning controls. There is, however, an interesting difference in the LPC response over anterior scalp sites in autistic subjects and cerebellar lesion subjects that may reflect the additional brain structural damage in autism. At frontal sites, cerebellar lesion subjects show a negligible LPC. Autism subjects, on the other hand, show a response that is not different in amplitude from control subjects, but in which the latency is significantly delayed. Whether this reflects an absent or merely a delayed response, the data show an extended positive response over frontal cortex while the control response (and that of cerebellar lesion subjects) over this time-course shows a frontal negativity following the LPC peak. This may be consistent with earlier findings of a failure to observe frontal attention-related negative ERP responses in autism [24], and could result from structural abnormalities of frontal cortex. A similar shift in LPC topography has also been reported in normal aging. One proposal is that the increased positivity at anterior sites in older individuals results from the attenuation of frontal negativities associated with loss of neural tissue in frontal cortex [41]. This could be true in autism as well.

4.2. The posterior late positive complex (LPC): context updating

The parietally-maximal LPC (P3b) was smaller for autism subjects than for controls over posterior, but not anterior scalp sites. Single trial analysis suggested that in autistic subjects compared to controls, the P3b was present on fewer trials and was reduced in amplitude when present. Unlike anterior electrode sites where peak latency of the LPC was longer for autism subjects than for controls, there were no latency differences over posterior electrode sites.

Because the P3b is reduced in amplitude in a variety of neurologic disorders as well as in normal aging, it is certainly possible that this electrophysiological abnormality reflects some non-specific process. Alternatively, the processes may be specific but difficult to identify given the limited information available from the averaged electrophysiological response. Given multiple sources and multiple potential influences from task-related antecedent sources, there are clearly many different ways in which brain pathology could affect this electrophysiological response. In autism, P3b abnormalities do appear to be both modality and task specific. The auditory P3b is consistently found to be abnormal in autistic individuals,

while in visual attention tasks in which the P3b is generated during a foveal discrimination the P3b is of normal amplitude. In contrast, this study and previous studies have found an attenuated P3b in autistic subjects during visual attention when the task was spatial in nature [119]. This seems quite consistent with behavioral visuo-spatial attention deficits in autism [52,116–118]. The reduced visuo-spatial P3b, like the delayed frontal LPC, may be associated with impaired spatial attention function and reflect abnormalities in the brain structures that support spatial attention. On this simple spatial detection task, autistic individuals were less accurate when attending the visual periphery, and the P3b was smaller during peripheral attention conditions as well.

The P3b is proposed to reflect processes subsequent to event-encoding or perceptual closure, and may represent context updating memory [40,54,72,114,120]. Of course, completion of a perceptual task would be likely to require a working memory update so that these operations would both be reflected in the LPC. Either model would be then be consistent with a recent imaging study that suggests the LPC reflects activity in a neural network that mediates working memory [90]. In a visuo-spatial attention task, these processes would involve the brain regions that subserve spatial attention, including regions important for spatial working memory processes. Cortical regions associated with spatial attention processing would be likely candidates for visuo-spatial P3b generators. The source generators for the P3b are unknown, but are likely to include multiple regions. Lesions of the temporal-parietal junction and the intraparietal sulcus may reduce the P3b, while lesions to other regions of frontal and parietal cortex do not [42,69,121]. Intracranial recordings suggest a source for the depth P3b in the hippocampus with related local cortical generators in regions including the superior temporal sulcus and the intraparietal sulcus [50]. Activation patterns during fMRI studies suggest that the intraparietal sulcus is, in fact, a critical component of spatial attention networks. Our recent studies with patients who have lesions to the intraparietal sulcus or to white matter underlying this sulcus, suggest that this region is also critical to the integrity of the scalp-recorded P3b response during spatial attention [42]. Abnormalities of parietal cortex including sulcal widening have been found in approximately 40% of individuals with autism [33]. This cortical abnormality could underlie the attenuation of the P3b in autistic subjects. Alternatively, the cerebellum may affect the generation of the P3b via disruption of the spatial attention process. In this case the cerebellar influence could be on local parietal P3b generators (such as the intraparietal sulcus) or could be on prefrontal regions which in turn affect the parietal generators. The visuo-spatial P3b has previously been reported to be reduced in amplitude in patients with cerebellar damage [2,128]. The P3b associated with this same spatial attention task as that used with autism subjects in this study was also reduced in patients with cerebellar lesions (see Fig. 7). In spatial attention function, the P3b may index the updating of spatial information following a target identification (e.g., refreshing or replacement of the representation of the relevant locations). The cerebellum is heavily interconnected with visuo-spatial attention regions, and has been implicated in spatial encoding of visual information [47,48]. One possibility then is that damage to the cerebellum may result in impaired spatial encoding. In the current task, that might mean difficulties maintaining a representation of attention locations which is required for accurate performance of the task. Tasks requiring more effortful attentional processing do generally result in reduced P3b amplitude [98]. Whatever the mechanism and the associated psychological construct, in spatial attention processing autism and cerebellar lesion patients do appear to have impaired performance and a reduced P3b.

5. Summary

We have found dissociations in abnormalities of frontal and posterior scalp recorded responses that suggest impairment in autism in two different component spatial attention processes (see Fig. 4). First, the latency of early fronto-central late positive complex response is delayed over frontal, but not over parietal regions. This abnormal component may index impaired spatial orienting. Second, the subsequent parietally-maximal late positive complex response is attenuated over parietal but not over frontal regions. This component may index impaired encoding or updating of spatial information in working memory. These electrophysiological abnormalities are consistent with behavioral evidence in autistic individuals of slow attention orienting and poor performance in tasks requiring attention to peripheral visual space. This suggests that the use of covert attention is compromised in autism.

The most consistently reported site of structural abnormality in the autistic brain is the cerebellum. However, additional brain regions that have documented abnormalities in autism include frontal and parietal cortex as well as the hippocampus. Although the functional deficits reported in this study may result from other structural abnormalities, there is compelling evidence to suggest that the cerebellum may affect these processes. First, patients with acquired lesions affecting only the cerebellum have abnormalities of the late positive scalp recorded response and behavioral attention deficits that parallel those of autistic individuals. Second, there is a significant relationship in normal function between the size of the posterior cerebellar vermis and the speed of orienting spatial attention. There is a complementary significant relationship between the size of the posterior vermal lobules and the latency of the early fronto-central LPC during spatial attention. This evidence suggests that damage to the cerebellum compromises use of covert attention.

Acknowledgements

Funded by NIMH 2RO1-MH36840 (EC) and NINDS 1RO1-NS34155 (JT).

References

[1] N.A. Akshoomoff, E. Courchesne, A new role for the cerebellum in cognitive operations, Behav. Neurosci. 106 (1992) 731–738.
[2] N.A. Akshoomoff, E. Courchesne, Intramodality shifting attention in children with damage to the cerebellum, J. Cogn. Neurosci. 6 (1994) 388–399.
[3] G. Allen, R.B. Buxton, E.C. Wong, E. Courchesne, Attentional activation of the cerebellum independent of motor involvement, Science 275 (1997) 1940–1943.
[4] American Psychiatric Association, 3rd Edition, Diagnostic and Statistical Manual of Mental Disorders : Dsm-iii-r, Vol. xxix, American Psychiatric Association, Washington, DC, 1987.
[5] American Psychiatric Association and American Psychiatric Association. Task Force on DSM-IV, 4th Edition, Diagnostic and Statistical Manual of Mental Disorders: Dsm-iv, Vol. xxvii, American Psychiatric Association, Washington, DC, 1994.
[6] R.A. Andersen, C. Asanuma, G. Essick, R.M. Siegel, Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule, J. Comp. Neurol. 296 (1990) 65–113.
[7] E. Attig, M.I. Botez, C. Hublet, C. Vervonck, J. Jacquy, A. Capon, Cerebral crossed diaschisis caused by cerebellar lesion: role of the cerebellum in mental functions, Revue Neurologique 147 (1991) 640–649.
[8] E.H. Aylward, N.J. Minshew, G. Goldstein, N.A. Honeycutt, A.M. Augustine, K.O. Yates, P.E. Barta, G.D. Pearlson, MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults, Neurology 53 (1999) 2145–2150.
[9] A. Bailey, P. Luthert, A. Dean, B. Harding, I. Janota, M. Montgomery et al., A clinicopathological study of autism, Brain 121 (1998) 889–905.
[10] M.L. Bauman, Microscopic neuroanatomic abnormalities in autism, Pediatrics 87 (1991) 791–796.
[11] M.L. Bauman, P.A. Filipek, T.L. Kemper, Early infantile autism, Int. Rev. Neurobiol. 41 (1997) 367–386.
[12] M.L. Bauman, T.L. Kemper (Eds.), Neuroanatomic observations of the brain in autism, in: The Neurobiology of Autism, John Hopkins University Press, Baltimore, 1994, pp. 119–145.
[13] A.J. Bell, T.J. Sejnowski, An information-maximization approach to blind separation and blind deconvolution, Neural Comput. 7 (1995) 1129–1159.
[14] G.J. Blatt, R.A. Andersen, G.R. Stoner, Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the Macaque, J. Comp. Neurol. 288 (1990) 421–445.
[15] M.I. Botez, T. Botez, R. Elie, E. Attig, Role of the cerebellum in complex human behavior, Ital. J. Neurol. Sci. 10 (1989) 291–300.
[16] M.I. Botez, J. Leveille, R. Lambert, T. Botez, Single photon emission computed tomography (SPECT) in cerebellar disease: cerebello-cerebral diaschisis, Eur. Neurol. 31 (1991) 405–412.
[17] R. Bracke-Tolkmitt, A. Linden, A.G. Canavan, B. Rockstroh, The cerebellum contributes to mental skills, Behav. Neurosci. 103 (1989) 442–446.
[18] R.A. Carper, E. Courchesne, Inverse correlation between frontal lobe and cerebellum sizes in children with autism, Brain 123 (2000) 836–844.
[19] L.L. Chao, R.T. Knight, Prefrontal deficits in attention and inhibitory control with aging, Cereb. Cortex 7 (1997) 63–69.
[20] K.T. Ciesielski, E. Courchesne, R. Elmasian, Effects of focused selective attention tasks on event-related potentials in autistic and normal individuals [published erratum appears in Electroencephalogr. Clin. Neurophysiol. 76(6) (1990) 566], Electroencephalogr. Clin. Neurophysiol. 75 (1990) 207–220.
[21] K.T. Ciesielski, R.J. Harris, B.L. Hart, H.F. Pabst, Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood, Neuropsychologia 35 (1997) 643–655.
[22] K.T. Ciesielski, J.E. Knight, Cerebellar abnormality in autism: a nonspecific effect of early brain damage?, Acta Neurobiol. Exp. 54 (1994) 151–154.
[23] J.T. Coull, A.C. Nobre, Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI, J. Neurosci. 18 (1998) 7426–7435.
[24] E. Courchesne, A neurophysiological view of autism, in: G.B. Mesibov, E. Schopler (Eds.), Neurobiological Issues in Autism, Plenum Publishing Corp, 1987, pp. 285–324.
[25] E. Courchesne, Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism [published erratum appears in Curr. Opin. Neurobiol. 7(4) (1997) 568], Curr. Opin. Neurobiol. 7 (1997) 269–278.
[26] E. Courchesne, N. Akshoomoff, J. Townsend, Recent advances in autism, Curr. Opin. Pediatr. 2 (1990) 685–693.
[27] E. Courchesne, H.J. Chisum, J. Townsend, A. Cowles, J. Covington, B. Egaas, M. Harwood, S. Hinds, G.A. Press, Parameters of brain development and aging from age 1.6 to 80 years based on quantitative analysis of in vivo MRI, Radiology 216 (2000) 672–682.
[28] E. Courchesne, S.A. Hillyard, R. Galambos, Stimulus novelty, task relevance and the visual evoked potential in man, Electroencephalogr. Clin. Neurophysiol. 39 (1975) 131–143.
[29] E. Courchesne, B.A. Kilman, R. Galambos, A.J. Lincoln, Autism: processing of novel auditory information assessed by event-related brain potentials, Electroencephalogr. Clin. Neurophysiol. 59 (1984) 238–248.
[30] E. Courchesne, A.J. Lincoln, B.A. Kilman, R. Galambos, Event-related brain potential correlates of the processing of novel visual and auditory information in autism, J. Autism Dev. Disord. 15 (1985) 55–76.
[31] E. Courchesne, A.J. Lincoln, R. Yeung-Courchesne, R. Elmasian, C. Grillon, Pathophysiologic findings in nonretarded autism and receptive developmental language disorder, J. Autism Dev. Disord. 19 (1989) 1–17.
[32] E. Courchesne, R.A. Müller, O. Saitoh, Brain weight in autism: normal in the majority of cases, megalencephalic in rare cases [see comments], Neurology 52 (1999) 1057–1059.
[33] E. Courchesne, G.A. Press, R. Yeung-Courchesne, Parietal lobe abnormalities detected with MR in patients with infantile autism [see comments], Am. J. Roentgenol. 160 (1993) 387–393.
[34] E. Courchesne, O. Saitoh, J.P. Townsend, R. Yeung-Courchesne, G.A. Press, A.J. Lincoln, R.H. Haas, L. Schriebman, Cerebellar hypoplasia and hyperplasia in infantile autism [letter], Lancet 343 (1994) 63–64.
[35] E. Courchesne, O. Saitoh, R. Yeung-Courchesne, G.A. Press, A.J. Lincoln, R.H. Haas, L. Schreibman, Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging, Am. J. Roentgenol. 162 (1994) 123–130.
[36] E. Courchesne, J. Townsend, O. Saitoh, The brain in infantile autism: posterior fossa structures are abnormal [see comments], Neurology 44 (1994) 214–223.
[37] E. Courchesne, J.P. Townsend, N.A. Akshoomoff, R. Yeung-Courchesne, G.A. Press, J.W. Murakami, A.J. Lincoln, H.E. James, O. Saitoh, A new finding: impairment in shifting attention in autistic and cerebellar patients, in: E.S.H. Broman, E.J. Grafman et al. (Eds.), Atypical Cognitive Deficits in Developmental Disorders:

Implications For Brain Function, Erlbaum, Hillsdale, NJ, USA, 1994, pp. 101–137.
[38] J.L. Cummings, Frontal-subcortical circuits and human behavior, Arch. Neurol. 50 (1993) 873–880.
[39] G. Dawson, C. Finley, S. Phillips, L. Galpert, A. Lewy, Reduced P3 amplitude of the event-related brain potential: it's relationship to language ability in autism, J. Autism Dev. Disord. 18 (1988) 493–504.
[40] E. Donchin, M.G. Coles, Is the p300 component a manifestation of context updating, Behav. Brain Sci. 11 (1988) 357–427.
[41] R.E. Dustman, R.Y. Emmerson, D.E. Shearer, Life span changes in electrophysiological measures of inhibition, Brain Cogn. 30 (1996) 109–126.
[42] E. Edwards, J. Townsend, M. Westerfield, S. Makeig, T.-P. Jung, Cortical lesions affect the late positive complex during visual-spatial attention, J. Cogn. Neurosci. 90 (Suppl.) (2000) 90, Abstract.
[43] P.K. Fehlow, E.A. Bernstein, Early infantile autism and excessive aerophagy with symptomatic megacolon and ileus in a case of Ehlers-Danlos syndrome, Padiatrie Grenzgebiete 31 (1993) 259–267.
[44] P.A. Filipek, Quantitative magnetic resonance imaging in autism: the cerebellar vermis, Curr. Opin. Neurol. 8 (1995) 134–138.
[45] G.R. Gaffney, L.Y. Tsai et al., Cerebellar structure in autism, Am. J. Dis. Child. 141 (1987) 1330–1332.
[46] M. Glickstein, N. Gerrits, I. Kralj-Hans, B. Mercier, J. Voogd, Visual pontocerebellar projections in teh macaque, J. Comp. Neurol. 349 (1994) 51–72.
[47] L. Goffart, D. Pelisson, Cerebellar contribution to the spatial encoding of orienting gaze shifts in the head-free cat, J. Neurophysiol. 72 (1994) 2547–2550.
[48] L. Goffart, D. Pélisson, Changes in initiation of orienting gaze shifts after muscimol inactivation of the caudal fastigial nucleus in the cat, J. Physiol. 503 (1997) 657–671.
[49] J. Grafman, I. Litvan, S. Massaquoi, M. Stewart, A. Sirigu, M. Hallett, Cognitive planning deficit in patients with cerebellar atrophy [see comments], Neurology 42 (1992) 1493–1496.
[50] E. Halgren, K. Marinkovic, P. Chauvel, Generators of the late cognitive potentials in auditory and visual oddball tasks, Electroencephalogr. Clin. Neurophysiol. 106 (1998) 156–164.
[51] E. Halgren, J.M. Stapleton, M.E. Smith, I. Altafullah, Generators of the human scalp P3s, in: R.Q.C.I. Bodis-Wollner (Ed.), Evoked Potentials, Liss, New York, 1986, pp. 269–289.
[52] N. Harris, E. Courchesne, J. Townsend, R.A. Carper, C. Lord, Neuroanatomic contributions to slowed orienting of attention in children with autism, Cogn. Brain Res. 8 (1999) 61–71.
[53] T. Hashimoto, M. Tayama, K. Murakawa, T. Yoshimoto, M. Miyazaki, M. Harada et al., Development of the brainstem and cerebellum in autistic patients, J. Autism Dev. Disord. 25 (1995) 1–18.
[54] G. Heit, M.E. Smith, E. Halgren, Neuronal activity in the human medial temporal lobe during recognition memory, Brain 113 (1990) 1093–1112.
[55] J.R. Holttum, N.J. Minshew, R.S. Sanders, N.E. Phillips, Magnetic resonance imaging of the posterior fossa in autism, Biol. Psychiatry 32 (1992) 1091–1101.
[56] T.P. Jung, C. Humphries, T.W. Lee, S. Makeig, M.J. McKeown, V. Iragui, T.J. Sejnowski, Extended ICA removes artifacts from electroencephalographic data, Adv. Neural Inform. Proc. Syst. 10 (1998) 894–900.
[57] T.P. Jung, C. Humphries, T.W. Lee, S. Makeig, M.J. McKeown, V. Iragui, T.J. Sejnowski, Removing electroencephalographic artifacts: Comparison between ICA and PCA, Neural Netw. Sign. Proc. VIII (1998) 63–72.
[58] T.P. Jung, S. Makeig, C. Humphries, T.W. Lee, M.J. McKeown, V. Iragui, T.J. Sejnowski, Removing encephalographic artifacts by blind source separation, Psychophysiology 37 (2000) 163–178.
[59] T.P. Jung, S. Makeig, M. Westerfield, J. Townsend, E. Courchesne, T.J. Sejnowski, Analyzing and visualizing single-trial event-related potentials, Adv. Neural Inform. Proc. Syst. 11 (1999) 118–124.
[60] T.P. Jung, S. Makeig, M. Westerfield, J. Townsend, E. Courchesne, T.J. Sejnowski, Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects, Clin. Neurophysiol. 111 (2000) 1745–1758.
[61] T.P. Jung, S. Makeig, M. Westerfield, J. Townsend, E. Courchesne, T.J. Sejnowski, Blind source separation of single-trial event-related potentials, IEEE Trans. Biomed. Eng., (in press).
[62] W.R. Kates, S.H. Mostofsky, A.W. Zimmerman, M.M. Mazzocco, R. Landa, I.S. Warsofsky, W.E. Kaufmann, A.L. Reiss, Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism, Ann. Neurol. 43 (1998) 782–791.
[63] C. Kemner, R.J. van der Gaag, M. Verbaten, H. van Engeland, ERP differences among subtypes of pervasive developmental disorders, Biol. Psychiatry 46 (1999) 781–789.
[64] S. Kimura, H. Nakamura, K. Matsumura, S. Morohashi, Y. Ueoka, A. Hasegawa, Y. Yonekura, Crossed 'cerebral' diaschisis? Seven cases with unilateral cerebellar vascular lesion which showed decreased perfusion in the contralateral cerebral cortex, Kaku Igaku Jpn. J. Nuclear Med. 26 (1989) 1259–1266.
[65] M.D. Kleiman, S. Neff, N.P. Rosman, The brain in infantile autism: are posterior fossa structures abnormal?, Neurology 42 (1992) 753–760.
[66] R. Knight, Neural mechanisms of event-related potentials: evidence from human lesion studies, in: J.W. Rohrbaugh, R. Parasuraman, R. Johnson (Eds.), Event-related Brain Potentials: Basic Issues and Applications, Oxford University Press, New York, 1990, pp. 3–18.
[67] R. Knight, Contribution of human hippocampal region to novelty detection, Nature 383 (1996) 256–259.
[68] R.T. Knight, Decreased response to novel stimuli after prefrontal lesions in man, Electroencephalogr. Clin. Neurophysiol. 59 (1984) 9–20.
[69] R.T. Knight, Distributed cortical network for visual attention, J. Cogn. Neurosci. 9 (1997) 75–91.
[70] R.T. Knight, M. Grabowecky, Escape from linear time: prefrontal cortex and conscious experience, in: M. Gazzaniga (Ed.), The Cognitive Neurosciences, MIT Press, Cambridge, MA, 1994, pp. 1357–1371.
[71] R.T. Knight, D. Scabini, D.L. Woods, C.C. Clayworth, Contributions of temporal-parietal junction to the human auditory P3, Brain Res. 502 (1989) 109–116.
[72] M. Kutas, G. McCarthy, E. Donchin, Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time, Science 197 (1977) 792–795.
[73] A. Le Couteur, M. Rutter, C. Lord, P. Rios, S. Robertson, M. Holdgrafer, J. McLennan, Autism diagnostic interview: a standardized investigator-based instrument, J. Autism Dev. Disord. 19 (1989) 363–387.
[74] T.H. Le, J.V. Pardo, X. Hu, 4t-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions, J. Neurophysiol. 79 (1998) 1535–1548.
[75] H.C. Leiner, A.L. Leiner, R.S. Dow, Does the cerebellum contribute to mental skills, Behav. Neurosci. 100 (1986) 443–454.
[76] H.C. Leiner, A.L. Leiner, R.S. Dow, Reappraising the cerebellum: what does the hindbrain contribute to the forebrain, Behav. Neurosci. 103 (1989) 998–1008.
[77] H.C. Leiner, A.L. Leiner, R.S. Dow, The human cerebro-cerebellar system: its computing, cognitive, and language skills, Behav. Brain Res. 44 (1991) 113–128.
[78] J.G. Levitt, R. Blanton, L. Capetillo-Cunliffe, D. Guthrie, A. Toga, J.T. McCracken, Cerebellar vermis lobules VIII-X in autism, Prog. Neuropsychopharmacology Biol. Psychiatry 23 (1999) 625–633.
[79] A.J. Lincoln, E. Courchesne, L. Harms, M. Allen, Contextual probability evaluation in autistic, receptive developmental language disorder, and control children: event-related brain potential evidence, J. Autism Dev. Disord. 23 (1993) 37–58.

[80] C. Lord, M. Rutter, P. DiLavore, Autism Diagnostic Observation Schedule, Western Psychological Services, Los Angeles, 1999.
[81] C. Lord, M. Rutter, S. Goode, J. Heemsbergen, H. Jordan, L. Mawhood, E. Schopler, Diagnostic observation schedule: a standardized observation of communicative and social behavior, J. Autism Dev. Disord. 19 (1989) 185–212.
[82] C. Lord, M. Rutter, A. Le Couteur, Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders, J. Autism Dev. Disord. 24 (1994) 659–685.
[83] S. Makeig, A.J. Bell, T.P. Jung, T.J. Sejnowski, Independent component analysis of electroencephalographic data, in: D. Touretzky, M. Mozer, M. Hasselmo (Eds.), Advances in Neural Information Processing Systems, Vol. 8, MIT Press, Cambridge, MA, 1996, pp. 145–151.
[84] S. Makeig, T.P. Jung, A.J. Bell, D. Ghahremani, T.J. Sejnowski, Blind separation of auditory event-related brain responses into independent components, Proc. Natl. Acad. Sci. USA 94 (1997) 10979–10984.
[85] S. Makeig, T.-P. Jung, S. Enghoff, T. Sejnowski, Software toolbox for analysis of psychophysiological data using Independent Component Analysis under Matlab, (1997).
[86] S. Makeig, M. Westerfield, T.P. Jung, J. Covington, J. Townsend, T.J. Sejnowski, E. Courchesne, Functionally independent components of the late positive event-related potential during visual spatial attention, J. Neurosci. 19 (1999) 2665–2680.
[87] S. Makeig, M. Westerfield, J. Townsend, T.P. Jung, E. Courchesne, T.J. Sejnowski, Functionally independent components of early event-related potentials in a visual spatial attention task, Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1999) 1135–1144.
[88] G.R. Mangun, S.A. Hillyard, Modulations of sensory-evoked brain potentials indicate changes in perceptual processing during visual-spatial priming, J. Exp. Psychol.: Hum. Percept. Perform. 17 (1991) 1057–1074.
[89] J. Martineau, B. Garreau, C. Barthelemy, G. Lelord, Evoked potentials and P300 during sensory conditioning in autistic children, Ann. N. Y. Acad. Sci. 425 (1984) 362–369.
[90] G. McCarthy, M. Luby, J. Gore, P. Goldman-Rakic, Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI, J. Neurophysiol. 77 (1997) 1630–1634.
[91] F.A. Middleton, P.L. Strick, Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function, Science 266 (1994) 458–461.
[92] F.A. Middleton, P.L. Strick, Dentate output channels: motor and cognitive components, Prog. Brain Res. 114 (1997) 553–566.
[93] J.W. Murakami, E. Courchesne, G.A. Press, R. Yeung-Courchesne, J.R. Hesselink, Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism, Arch. Neurol. 46 (1989) 689–694.
[94] B. Novick, D. Kurtzberg, H.G. Vaughn Jr., An electrophysiological indication of defective information storage in childhood autism, Psychiatry Res. 1 (1979) 101–108.
[95] B. Novick, H.G. Vaughn Jr., D. Kurtzberg, R. Simson, An electrophysiological indication of auditory processing defects in autism, Psychiatry Res. 3 (1980) 107–114.
[96] R.D. Oades, M.K. Walker, L.B. Geffen, L.M. Stern, Event-related potentials in autistic and healthy children on an auditory choice reaction time task, Int. J. Psychophysiol. 6 (1988) 25–37.
[97] M. Onofrj, L. Curatola, G. Malatesta, P. Colamartino, S. Bazzano, T. Fulgente, F. Ferracci, Delayed P3 event-related potentials (ERPs) in thalamic hemorrhage, Electroencephalogr. Clin. Neurophysiol. 83 (1992) 52–61.
[98] T.W. Picton, The P300 wave of the human event-related potential, J. Clin. Neurophysiol. 9 (1992) 456–479.
[99] J. Piven, E. Nehme, J. Simon, P. Barta, G. Pearlson, S.E. Folstein, Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle, Biol. Psychiatry 31 (1992) 491–504.
[100] J. Piven, K. Saliba, J. Bailey, S. Arndt, An MRI study of autism: the cerebellum revisited [see comments], Neurology 49 (1997) 546–551.
[101] J. Polich, Meta-analysis of P300 normative aging studies, Psychophysiology 33 (1996) 334–353.
[102] J. Polich, J.E. Alexander, L.O. Bauer, S. Kuperman, S. Morzorati, S.J. O'Connor, B. Porjesz, J. Rohrbaugh, H. Begleiter, P300 topography of amplitude/latency correlations, Brain Topogr. 9 (1997) 275–282.
[103] J. Polich, L. Squire, P300 from amnesiac patients with bilateral hippocampal lesion, Electroencephalogr. Clin. Neurophysiol. 86 (1993) 408–417.
[104] M.I. Posner, Y. Cohen, Component of performance, in: H. Bouma, D.G. Bouhuis (Eds.), Attention and Performance, Erlbaum, Hillsdale, NJ, 1984, pp. 531–556.
[105] W.S. Pritchard, N. Raz, G.J. August, Visual augmenting/reducing and P300 in autistic children, J. Autism Dev. Disord. 17 (1987) 231–242.
[106] E.R. Ritvo, B.J. Freeman et al., Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC Autopsy Research Report, Am. J. Psychiat. 143 (1986) 862–866.
[107] M. Rousseaux, M. Steinling, Crossed hemispheric diaschisis in unilateral cerebellar lesions, Stroke 23 (1992) 511–514.
[108] O. Saitoh, E. Courchesne, B. Egaas, A.J. Lincoln, L. Schreibman, Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities, Neurology 45 (1995) 317–324.
[109] O. Saitoh, C. Karns, E. Courchesne, Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism, Brain, (in press).
[110] J.D. Schmahmann, D. Pandya, Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey, J. Comp. Neurol. 289 (1989) 53–73.
[111] J.D. Schmahmann, D.N. Pandya, The cerebrocerebellar system, Int. Rev. Neurobiol. 41 (1997) 31–60.
[112] J.D. Schmahmann, J.C. Sherman, Cerebellar cognitive affective syndrome, Int. Rev. Neurobiol. 41 (1997) 433–440.
[113] E. Schopler, R. Reichler, R. De Velis, K. Daly, Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS), J. Autism Dev. Disord. 10 (1980) 91–103.
[114] H.T. Schupp, W. Lutzenberger, H. Rau, N. Birbaumer, Positive shifts of event-related potentials: a state of cortical disfacilitation as reflected by the startle reflex probe, Electroencephalogr. Clin. Neurophysiol. 90 (1994) 135–144.
[115] N.K. Squires, K.C. Squires, S.A. Hillyard, Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man, Electroencephalogr. Clin. Neurophysiol. 38 (1975) 387–401.
[116] J. Townsend, E. Courchesne, J. Covington, M. Westerfield, N.S. Harris, P. Lyden, T.P. Lowry, G.A. Press, Spatial attention deficits in patients with acquired or developmental cerebellar abnormality, J. Neurosci. 19 (1999) 5632–5643.
[117] J. Townsend, E. Courchesne, B. Egaas, Slowed orienting of covert visual-spatial attention in autism: specific deficits associated with cerebellar and parietal abnormality, Dev. Psychopathol. 8 (1996) 503–584.
[118] J. Townsend, N.S. Harris, E. Courchesne, Visual attention abnormalities in autism: delayed orienting to location, J. Int. Neuropsychol. Soc. 2 (1996) 541–550.
[119] M.N. Verbaten, J.W. Roelofs, H. Van Engeland, J.K. Kenemans, Abnormal visual event-related potentials of autistic children, J. Autism Dev. Disord. 21 (1991) 449–470.
[120] R. Verleger, Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of p3, Behav. Brain Sci. 11 (1988) 343–356.

[121] R. Verleger, W. Heide, C. Butt, D. Koempf, Reduction of P3-sub(b) in patients with temporo-parietal lesions, Cogn. Brain Res. 2 (1994) 103–116.
[122] C.-W. Wallesch, A. Horn, Long-term effects of cerebellar pathology on cognitive functions, Brain Cogn. 14 (1990) 19–25.
[123] G.R. Wells, M.J. Hardiman, C.H. Yeo, Visual projections to the pontine nuclei in the rabbit: orthograde and retrograde tracing studies with WGA–HRP, J. Comp. Neurol. 279 (1989) 629–652.
[124] M. Westerfield, J. Townsend, E. Edwards, S. Makeig, T.-P. Jung, E. Courchesne, Cerebellar lesions affect the late positive complex in visual spatial attention [Abstract], J. Cogn. Neurosci. 98 (Suppl.) (2000) 98.
[125] M. Westerfield, J. Townsend, S. Makeig, T.J. Sejnowski, E. Courchesne, Independent components of the late positive event-related potential in a visual spatial attention task: normal and clinical subject differences [Abstract], Soc. Neurosci. Abstr. 24 (1998) 507.
[126] M.N. Westerfield, J. Townsend, T.-P. Jung, E. Courchesne, The endogenous ERP is reduced following cerebellar damage, especially over frontal cortex, Brain (submitted for publication).
[127] R.S. Williams, S.L. Hauser et al., Autism and mental retardation: neuropathologic studies performed in four retarded persons with autistic behavior, Arch. Neurol. 37 (1980) 749–753.
[128] S. Yamaguchi, H. Tsuchiya, S. Kobayashi, Visuospatial attention shift and motor responses in cerebellar disorders, J. Cogn. Neurosci. 10 (1998) 95–107.